Influenza (Including FluMist)

In this segment of the program we will talk about influenza vaccine. We will begin with a discussion of the 2003 influenza vaccine ACIP recommendations. Following this, we will talk about the new live attenuated influenza vaccine, FluMist.

More than fifty years after the introduction of an effective vaccine, influenza continues to take an enormous toll in lost lives and health care costs.

Influenza is the most frequent cause of death from a vaccine preventable disease in the United States. During 1990 through 1999, approximately 36 thousand influenza- associated pulmonary and circulatory deaths occurred during each influenza season. Influenza seasons in which H3N2 viruses predominate are associated with higher mortality. Persons 65 years and older account for more than 90 percent of deaths attributed to pneumonia and influenza. People with underlying medical conditions account for most of the remaining 10 percent of deaths.

In addition to fatalities, influenza is also responsible for an average of 114 thousand hospitalizations per year. Although persons 65 years and older are at the highest risk of dying from influenza, other age groups are at nearly as high risk for influenza-associated hospitalization.

This table summarizes age-specific rates of influenza related hospitalizations per 100 thousand population from several published studies. The rates among people at high risk of complications are shown in the center column, and those not at high risk in the right column.

Children birth to 4 years of age had rates of hospitalization higher than any other age group through age 64. The hospitalization rate among children younger than 4 years was 500 per 100 thousand population, 5 times higher than healthy children of the same age. This rate of hospitalization was higher than any other age group with high risk conditions through age 64, and in some of the studies even higher than people 65 years and older with high risk conditions.

The risk of complications and hospitalization is not equal for all children. This table shows rates of influenza related hospitalizations by age of a Medicaid population in Tennessee. By far the highest rates of hospitalization were among children 11 months of age and younger, particularly those with high risk conditions, shown in the center column. But rates of hospitalization are very high through 2 years of age in both healthy children and those with high risk conditions. Rates of hospitalization in children younger than 2 years are similar to those of persons 65 and older with high risk medical conditions.

For several years, the Advisory Committee on Immunization Practices and the American Academies of Pediatrics and Family Physicians have been discussing options to reduce the burden of influenza among young children.

Beginning in the 2002-2003 influenza season, and continuing this year, providers are encouraged to administer influenza vaccine to children 6 months to 23 months of age when feasible. In addition, vaccination is encouraged for the household contacts and out of home caregivers of children twenty three months of age and younger. This is particularly important for household contacts of infants younger than six months of age because no influenza vaccine is approved for this age group in the United States.

This recommendation is the first step toward routine annual influenza vaccination of young children. It is likely that ACIP and the Academies will make a full recommendation for administration of influenza vaccine to ALL children six to twenty three months of age within the next three years.

If you provide healthcare services to children, you should begin thinking about how to integrate annual influenza vaccination into your practice. At the very least, you should be vaccinating children 6 months and older who have underlying medical conditions. This will help acclimate your office to a seasonal vaccine, and get ready for the day when influenza vaccine becomes a part of routine childhood vaccination.

For the 2003- 2004 influenza season, the Vaccines for Children, or VFC program will provide coverage for influenza vaccine for healthy children 6 to 23 months of age. VFC will also provide vaccine for children 2 to 18 years of age who are household contacts of children 2 years of age and younger.

ACIP updates it's influenza vaccine recommendations every year. This year's ACIP statement was published in April 2003.

The most significant changes in this year's recommendations are the timing of influenza vaccination by age and risk group; the 2003-2004 vaccine virus strains; and the increased availability of influenza vaccine with reduced thimerosal content. There is also information concerning influenza vaccine for children 6 to 23 months of age, which we discussed earlier.

As you are aware, there were substantial delays in the distribution of influenza vaccine in 2000 and 2001. In response, ACIP has recommended a tiered influenza vaccination program, with high risk persons to be vaccinated in October, and healthy people vaccinated later. However, on August 11, 2003, CDC determined that vaccine production for the 2003-2004 influenza season is proceeding satisfactorily. Projected production and distribution schedules will allow for sufficient supply of influenza vaccine during October and November.

As a result, for the 2003-2004 influenza season, vaccination can proceed for all high risk AND healthy persons, individually and through mass campaigns, as soon as vaccine is available. A tiered influenza vaccination schedule is not necessary in 2003.

To avoid missed opportunities for vaccination of persons at high risk for serious complications, such persons should be offered vaccine beginning in September during routine healthcare visits or during hospitalizations, if vaccine is available. In facilities housing older persons, such as long term care facilities, vaccination before October should be avoided because antibody levels in such persons can begin to decline within a few months after vaccination. ACIP does NOT recommend a second dose of vaccine in the same season, even if the first dose was given in September.

There seems to be a perception that influenza vaccination is an October activity. It has been difficult to convince providers to continue providing vaccine to their patients into December and beyond. It is critical that we change this perception.

This graph shows the month in which influenza activity peaked in the United States from 1976 through 2002. Influenza activity peaked in December in only 15 percent of seasons. Activity peaked in January in 23 percent of seasons and in February in 42 percent of seasons. The message here is that December is NOT too late to receive influenza vaccine. Vaccination in January or even February can still prevent a lot of influenza.

ACIP recommends that providers should continue to offer influenza vaccine, especially those at high risk of complications, and to healthcare workers in December. Providers should continue to vaccinate throughout influenza season as long as vaccine is available, even after influenza activity has been documented in the community.

Let’s review briefly groups at increased risk for complications of influenza. Age is an important risk factor, particularly for those 65 years and older, and children less than 24 months of age. In addition to age, the medical conditions that increase the risk of influenza complications include: pulmonary disease such as emphysema and asthma; cardiovascular disease; and metabolic disease such as diabetes. Additionally, renal dysfunction, like chronic renal failure or nephropathy; hemoglobinopathy, like sickle cell disease; and immunosuppression, including HIV are high risk conditions. In addition to people with chronic illnesses, other risk groups include residents of long term care facilities and persons 6 months to 18 years of age receiving chronic aspirin therapy because of the risk of Reye syndrome. Finally, most pregnant women are recommended to be routinely vaccinated - specifically those who will be in the second or third trimester of pregnancy during influenza season.

Healthcare workers are at increased risk of exposure to influenza. Also, a healthcare worker with influenza could expose many patients who are at high risk of complications of influenza. So healthcare workers are a high priority for early supplies of influenza vaccine. Yet in 2001, only about 36 percent of healthcare workers reported having been vaccinated in the previous year. Healthcare workers- ALL healthcare workers- owe it to their patients to receive annual influenza vaccine. You and you staff should each receive a dose of the very first shipment of vaccine you receive each year.

The majority of the influenza vaccine available in the U.S. is inactivated subunit vaccine. The two types of subunit vaccine available contain either split virus, or purified hemagglutinin. A live attenuated influenza vaccine administered by nasal spray is also available for the first time this year. We will discuss this vaccine in more detail in a few minutes. All available influenza vaccines – including the live attenuated vaccine- are trivalent- meaning they contain 3 different viruses, two type A viruses and one type B. The viruses contained in the vaccine are chosen each spring, based on surveillance of current circulating strains.

The vaccine recommended for the 2003- 2004 season includes A/Moscow/10/99- the H3N2 strain; A/New Caledonia/20/99- the H1N1 strain, and B/Hong Kong/330/2001. For the A/Moscow virus, manufacturers will use the antigenically equivalent A/Panama/2007/99 strain. A different, antigenically equivalent B strain may be substituted for the B/Hong Kong antigen. These viruses will be used because of their growth properties and because they are representative of influenza viruses likely to circulate in the United States during the 2003-2004 influenza season.

You might have noticed that the influenza strains chosen for the 2003-2004 vaccine are the same strains that were in the 2002-2003 vaccine. Although one or two strains are generally changed each year, the same strains are retained for 2 or more years once or twice per decade, most recently in 1998 and 1999. There are two important points to make about this.

Although the strains are the same as in last year's vaccine, do NOT use the 2002-2003 vaccine you might still have in your refrigerator. All of the 2002-2003 influenza vaccine expired on June 30, 2003. Expired vaccine should NEVER be administered. Second, although the strains are the same as last year, your patients – and YOU- still need a dose of influenza vaccine this year, even if you had a dose last year. Antibody from last years dose has waned, and you need the boost from this years vaccine to be sure your patients – and YOU – remain protected.

The inactivated influenza vaccination schedule is relatively simple – one INTRAMUSCULAR dose per year. But the dose is not the same for all age groups, and some recipients need 2 doses.

Here is the routine schedule for influenza vaccine. The minimum age is 6 months. No influenza vaccine is approved for children younger than 6 months. Children 6 months through 35 months of age receive a dose of zero point 25 milliliter- half the dose of an older child and adult. Recipients 3 years of age and older should receive a one-half milliliter dose. Children 6 months trough 8 years of age receiving influenza vaccine for the FIRST time should receive TWO doses, separated by one month. The first dose is an immunologic primer. Two doses are not necessary for people 9 years or older, because by this age our immune systems have been primed the hard way- with wild influenza virus.

What if a child is receiving influenza vaccine for the first time, and does not return for the second dose a month later. Does the child need one or two doses the following year? You can count last year's dose as the primer. The child needs only one dose this year, and in subsequent years. The schedule for live attenuated influenza vaccine is similar to that for inactivated vaccine. We will discuss this more in a moment.

All influenza vaccine is made from highly purified, egg grown viruses. Because the vaccine viruses are initially grown in embryonated hens' eggs, the vaccine might contain a small amount of residual egg protein. Live attenuated influenza vaccine contains a substantial amount of egg protein. Consequently, influenza vaccine should not be administered to persons with anaphylactic egg allergy.

For the 2003- 2004 influenza season, a limited number of doses of reduced thimerosal content influenza vaccine will be available. The reduced thimerosal formulations contain less than 1 microgram of thimerosal per dose, compared to 25 micrograms per dose for regular influenza vaccine. Reduced thimerosal formulations are available from both manufacturers.

The Evans vaccine – Fluvirin – is approved by FDA for persons 4 years of age and older. It should not be administered to children 6 months to 4 years of age. The Aventis Pasteur vaccine –Fluzone – is available in two forms – a 0.25 milliliter single dose package for children 6 to 35 months of age, and a 0.5 milliliter single dose package for children 3 years of age and older.

ACIP believes that because of the known risks for severe illness from influenza infection, the benefit of influenza vaccine with reduced OR STANDARD thimerosal content outweighs the theoretical risk, if any, from thimerosal. The removal of thimerosal from other vaccines further reduces the theoretical risk from thimerosal in influenza vaccines.

Influenza vaccine has been available in the United States since the mid-1940s. Until recently, all influenza vaccines contained either whole inactivated virus, or

virus subunits. In June 2003, the Food and Drug Administration approved this country's first live attenuated influenza vaccine, which we will refer to as LAIV. The vaccine is produced by MedImmune and marketed under the name FluMist. It will be distributed by Wyeth Vaccines.

LAIV has several unique properties in addition to being a live virus vaccine. The live influenza viruses in the vaccine are attenuated, and produce mild or no signs or symptoms related to influenza virus infection. They are temperature sensitive, which means they do not replicate efficiently at 38 to 39 degrees centigrade. This property prevents the live viruses from replicating efficiently in the lower airways. The viruses are also cold adapted, which means they replicate efficiently at the temperature of the upper airway, 25 degrees centigrade. This temperature is permissive for replication of LAIV viruses but restrictive for replication of many wild type viruses.

What this means is that LAIV is able to replicate in the mucosa of the nasopharynx, which produces protective immunity against the viruses in the vaccine. On the other hand, the viruses are attenuated and do not replicate effectively in the lung, so they cannot produce influenza disease. LAIV is trivalent, and contains the same virus strains included in inactivated influenza vaccine. LAIV does not contain thimerosal or gelatin.

LAIV has been tested in groups of both healthy children and healthy adults. A randomized, double-blind, placebo-controlled trial in healthy children 60 to 84 months of age assessed the efficacy of the trivalent LAIV against culture confirmed influenza during two influenza seasons.

In year one, when vaccine and circulating virus strains were well matched, efficacy was 87 percent against culture confirmed influenza. In year two, when the type A component was not well matched between vaccine and circulating virus strains, efficacy was also 87 percent. Other results from this trial included a 27 percent reduction in febrile otitis media and a 28 percent reduction in otitis media with concomitant antibiotic use. Receipt of LAIV also resulted in decreased fever and otitis media in vaccine recipients who developed influenza.

A randomized, double-blind, placebo-controlled trial among 3,920 healthy working adults aged 18 to 49 years assessed several endpoints, including reductions in illness, absenteeism, health care visits, and medication use during influenza outbreak periods. This study was conducted during the 1997-98 influenza season, when the vaccine and circulating type A strains were not well matched. This study did not include laboratory virus testing of cases.

During peak outbreak periods, there was no significant reduction in febrile episodes between adult LAIV and placebo recipients. However, LAIV recipients

had 24 percent fewer febrile upper respiratory illness episodes, and 27 percent fewer lost work days due to febrile upper respiratory illness. Days of antibiotic use were reduced by 41 to 45 percent in vaccine recipients.

The ability of LAIV and inactivated influenza vaccine to protect adults against influenza illness after experimental challenge with wild type influenza virus has also been studied. The overall efficacy of LAIV in preventing laboratory documented influenza from all three influenza strains combined was 85 percent. The efficacy was 71 percent among inactivated vaccine recipients. The difference between the two vaccines was not statistically significant.

So, LAIV appears to reduce febrile upper respiratory tract episodes, lost work days, and antibiotic use among adult recipients. However, there is no evidence at this time that LAIV reduces febrile illness or culture confirmed influenza more effectively than inactivated influenza vaccine.

LAIV contains live influenza viruses. As a result, there is a potential for transmission of these viruses from vaccinees to other persons.

Vaccinated children can shed vaccine viruses in nasopharyngeal secretions for up to 3 weeks. In one study in a daycare setting, 80 percent of vaccinated children 8 to 36 months of age shed at least one virus strain for an average of 7.6 days. In this study, one instance of transmission of vaccine virus to a contact was documented. The transmitted virus retained it's attenuated, cold-adapted, temperature-sensitive characteristics. The frequency of shedding of vaccine strains by persons 5 to 49 years of age has not been determined.

Because of the potential for shedding and transmission of vaccine virus by healthy adolescents and adults, ACIP prefers that LAIV NOT be administered to people in close contact with immunosuppressed persons, including healthcare workers. We will discuss this issue again in a few minutes.

The safety of the approved LAIV has been assessed in 20 pre-licensure clinical trials. More than 6 thousand study participants were in the approved age range of 5 to 49 years.

Among healthy children, there were no significant differences between vaccine and placebo recipients in the proportion with upper respiratory symptoms such as runny nose and nasal congestion, fever, or other systemic symptoms. These symptoms were reported in 10 to 40 percent of both vaccine and placebo recipients. Data from an unpublished study suggested a significantly increased risk of asthma or reactive airways disease among children 12 to 59 months of age who received LAIV. Because of this, LAIV is not approved for use in children

less than 60 months of age, and it should not be used in persons with asthma, reactive airways disease, or other chronic pulmonary diseases.

Among healthy adults, a significantly increased rate of cough, runny nose, nasal congestion, sore throat, and chills was reported among vaccine recipients. These symptoms were reported in 10 to 40 percent of vaccine recipients, and generally 3 to 10 percent higher than in placebo recipients. There was no increase in the occurrence of fever among vaccine recipients. No serious adverse reactions have been identified in LAIV recipients, either children or adults.

There have been no instances of Guillian Barre Syndrome reported among LAIV recipients. However the number of persons vaccinated to date is too small to identify such a rare vaccine adverse reaction. The risk of GBS among recipients of inactivated influenza vaccine is estimated to be in the range of one or two cases per million doses administered.

There are few data concerning the safety of LAIV among persons at high risk for development of complications of influenza, such as immunosuppressed persons or those with chronic pulmonary or cardiac disease. Until additional data is available, persons at high risk of complications of influenza should NOT receive LAIV. These persons should continue to receive inactivated influenza vaccine.

LAIV may be a useful adjunct to the influenza vaccination of healthy people, but is not a replacement for inactivated vaccine.

Influenza virus infections cause significant morbidity and mortality in the United States each year. Prevention of influenza relies primarily on annual vaccination. For more than 50 years, only inactivated influenza vaccine administered by injection was available for use in the United States. In 2003, a live attenuated influenza vaccine, or LAIV, became available for the first time in the United States. This vaccine will be marketed under the brand name of FluMist. Unlike inactivated vaccine, this new vaccine is administered by a nasal spray.

LAIV is similar to inactivated influenza vaccine in several ways. Both vaccines contain the same strains of influenza viruses: two strains of influenza A virus, and one B virus. Virus strains for both influenza vaccines are selected annually. Viruses for both vaccines are grown in eggs. Finally, both vaccines should be administered annually to provide optimal protection against influenza infection.

LAIV has several potential advantages over inactivated influenza vaccine. Because it is a live vaccine, it could induce a more broad mucosal and systemic immune response than inactivated vaccine. Other advantages include its ease of administration, and the acceptability of an intranasal rather than intramuscular route of administration.

The Advisory Committee on Immunization Practices, or ACIP, discussed the use of LAIV at length at it's June 2003 meeting. ACIP believes that LAIV may be an important adjunct to the use of inactivated influenza vaccine. However, LAIV will NOT be a substitute for inactivated influenza vaccine, particularly among the groups at highest risk of complications of influenza. This is because LAIV has several important limitations. The most important limitation is that LAIV is currently approved for use ONLY among healthy persons 5 years through 49 years of age. This means that it should not be used in young children, or persons 50 years of age and older. It also should not be used in anyone with an underlying medical condition that increased the person's risk of complications of influenza. Inactivated influenza vaccine should be used for these groups.

A second limitation is that because the vaccine virus is live, it cannot be given to pregnant women or to immunosuppressed persons, as with other live vaccines. Women in the second or third trimester of pregnancy during influenza season, and immunosuppressed people should receive only inactivated influenza vaccine.

A third limitation of LAIV is that the live influenza vaccine virus is shed from the nasopharynx of vaccine recipients for as long as 3 weeks after vaccination. Transmission of vaccine virus from person to person has been documented.

There are currently no data assessing the risk of transmission of LAIV from vaccine recipients to immunosuppressed contacts. In the absence of such data, use of inactivated influenza vaccine is preferred for vaccinating household members, healthcare workers, and others who have close contact with immunosuppressed individuals because of the theoretical risk that a live attenuated vaccine virus could be transmitted to the immunosuppressed individual and cause disease.

Finally, LAIV has very stringent storage and handling requirements, and is significantly more expensive than inactivated influenza vaccine.

Live attenuated influenza vaccine may help improve influenza vaccine coverage rates among healthy people 5 through 49 years of age – groups with historically very low rates of influenza vaccination. But LAIV is NOT a substitute for inactivated influenza vaccine among persons at high risk of complications of influenza. We will continue to depend on inactivated influenza vaccine to protect these high risk groups.

ACIP has prepared supplemental recommendations on the use of LAIV. These recommendations are being finalized now, and should be published this fall.

Live attenuated influenza vaccine is approved by the Food and Drug Administration ONLY for use among healthy persons 5 through 49 years of age. This group, including most persons in close contact with high risk groups, and

those wishing to reduce their risk of influenza, now have the option for choosing either inactivated vaccine or LAIV.

This table shows the vaccination schedule for LAIV based on age and prior influenza vaccination history. A dose of LAIV is 0.5 milliliter, regardless of age, divided equally between nostrils. Children 5 to 8 years of age who have received NO previous influenza vaccine- either LAIV or inactivated influenza vaccine- should receive two doses of LAIV separated by 6 to 10 weeks. Note that this is longer than the 4 weeks recommended between the first two doses of inactivated influenza vaccine. ACIP recommends that children 5 to 8 years of age previously vaccinated at any time with either LAIV or inactivated influenza vaccine receive one dose of LAIV. They do not require a second dose. This is different than the manufacturer's labeling, which recommends that children who have not previously received LAIV should receive two doses, regardless of whether they may have previously received inactivated influenza vaccine. Persons 9 through 49 years of age should receive one dose of LAIV.

LAIV is approved for use ONLY in healthy persons 5 through 49 years of age. Consequently, LAIV is NOT approved, and is not recommended for administration to most people for whom inactivated influenza vaccine has been recommended for many years.

Persons who should NOT receive LAIV include children less than 5 years of age; persons 50 years of age and older; persons with asthma, reactive airways disease or other chronic pulmonary or cardiovascular conditions. These persons should receive inactivated influenza vaccine.

Persons with other underlying medical conditions should not receive LAIV. These conditions include metabolic disease such as diabetes, renal disease, or hemoglobinopathy, such as sickle cell disease; and children or adolescents receiving chronic therapy with aspirin or other salicylates, because of the association of Reye syndrome with wild-type influenza infection. Persons in these groups should receive inactivated influenza vaccine.

As with all live virus vaccines, persons who are immunosuppressed because of disease, including HIV, or who are receiving immunosuppressive therapy, should not receive LAIV. Pregnant women should not receive LAIV. Immunosuppressed persons and pregnant women should receive inactivated influenza vaccine. Since LAIV contains residual egg protein, it should not be administered to persons with a history of severe allergy to egg or any other vaccine component. Finally, the vaccine should not be administered to a person with a history of Guillain-Barré syndrome.

Close contacts of persons at high risk for complications from influenza should receive influenza vaccine. This reduces the risk of transmission of wild-type

influenza viruses to high risk individuals. There are no data assessing the risk of transmission of LAIV from vaccine recipients to immunosuppressed contacts.

In the absence of such data, use of inactivated influenza vaccine is preferred for vaccinating household members, healthcare workers, and others who have close contact with immunosuppressed individuals. This preference is because of the theoretical risk that a live attenuated vaccine virus could be transmitted to the immunosuppressed individual and cause disease. ACIP states no preference between inactivated vaccine and LAIV for vaccination of healthy persons aged 5 to 49 years in close contact with all other high-risk groups.

LAIV can be administered to persons with minor acute illnesses, such as mild upper respiratory tract infection with or without fever. However, if clinical judgment suggests nasal congestion is present which might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness.

The manufacturer's package insert recommends that LAIV not be administered concurrently with other vaccines. This is because it is not known whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine. In the absence of specific data indicating interference, ACIP recommends that providers follow the simultaneous administration guidelines published in the General Recommendations on Immunization.

Inactivated vaccines do not interfere with the immune response to live vaccines. Inactivated vaccines – such as pneumococcal polysaccharide or tetanus and diphtheria toxoids – can be administered either simultaneously or at any time before or after LAIV. Other live vaccines can be administered at the same visit as LAIV. However, live vaccines not administered on the same day should be administered at least 4 weeks apart when possible.

LAIV is stored and administered unlike any other vaccine you have ever encountered. We would like to spend a few minutes on this aspect of LAIV to familiarize you with it. First, here is a short video produced by MedImmune that describes how the vaccine is shipped and stored.

> Flumist is shipped to your office via overnight delivery. You'll receive an e-mail or a fax the day before to let you know that FluMist will arrive in your office at approximately 10:30 a.m. the next day. When FluMist arrives at your office, there are three things you should do. First, open the carton and check the watermark indicator to make sure FluMist hasn't thawed in shipping. Then, immediately put FluMist away, either in your FluMist box or in your manual defrost freezer. Lastly,

dispose of the dry ice in the carton according to the instructions on the dry ice packaging.

If any red is showing in the warm mark indicator, do not use the FluMist. Call Wyeth products quality for further instructions. Save all materials except for the dry ice until further instructed by products quality. This booklet, your guide to handling and storing FluMist, has all the details on storage and handling. You will get a copy from your Wyeth vaccines or FluMist sales representative.

Storage and handling of LAIV is critical, so we would like to reiterate a couple of important points. The viruses in LAIV have no tolerance for heat.

LAIV must be stored at or below minus 15 degrees Centigrade, which is 5 degrees Fahrenheit at all times. The vaccine cannot tolerate storage temperature warmer than minus 15 degrees. So LAIV cannot be stored in a frost-free freezer. This is because the temperature in a frost-free freezer may rise above minus 15 degrees centigrade during the defrost cycle. LAIV must be stored ONLY in a manual defrost freezer that can reliably maintain minus 15 degrees centigrade. If you do not have access to a manual defrost freezer, then you must store LAIV in a special manufacturer-supplied freezer box.

Here is a freezer box. It is about 15 inches wide by 9 and a half inches deep, by 8 and a half inches high, and weighs about 19 pounds. The box has a hinged door with a latch. It has the capacity to hold 8 boxes of 10 sprayers each, or 80 doses total. The manufacturer recommends that no other vaccines or other products be kept in the box. The walls of the freezer box contain a special gel that will protect the vaccine from temperature fluctuations in a frost-free freezer. The freezer box must be placed in the freezer for at least 4 days before it is ready to store LAIV. You can place it in the corner of the freezer, as shown here. Instructions for using the freeze box are included in the packaging, and are also printed on the front of the door of the box. As you can see here, the first instruction is to turn down the temperature of the freezer to it’s lowest setting. You must be EXTREMELY careful when you do this.

The temperature of the freezer compartment can affect the temperature of the refrigerator compartment. By lowering the temperature of the freezer, you risk lowering the refrigerator temperature below 32 degrees Fahrenheit, and freezing everything in the refrigerator, including vaccines. With the exception of MMR, refrigerated vaccines that are frozen must be destroyed.

If you lower the temperature of your freezer, you MUST do it early in the morning of a work day. The temperature in both the freezer AND refrigerator must be monitored frequently. You must NOT lower the temperature and then go home for the night, or for the weekend because of the risk of destroying the vaccines in your refrigerator. This would be a very costly mistake.

LAIV will be shipped to you frozen on dry ice. Each box contains 2 preformed sealed trays, like you see here. Each tray contains 5 prefilled sprayers of vaccine.

In general, you will keep the vaccine frozen until immediately before it is used, at which time you will thaw it in your hand. LAIV may also be thawed in a refrigerator. However, it can be stored at refrigerator temperature – which is 2 to 8 degrees centigrade for no more than 24 hours prior to use. Any LAIV that is kept at refrigerator temperature more than 24 hours must be discarded.

The sprayer is not just a modified syringe. It is a specially designed device with a special one-way aerosol dispersion tip that produces a fine mist. The plastic clip on the plunger divides the dose in half. One half of each dose is sprayed, or misted, into each nostril.

The tip is designed to produce a large particle aerosol that is deposited in the nose and nasopharynx. Some droplets may drip down from the nose, but the majority are cleared by mucocilliary flow into the oropharyngeal tract. Less than 1 percent of the droplets reach the lower airways.

We thought you might want to see what the mist looks like as it comes out of the sprayer. We shot this video using the sprayer loaded with water. You definitely don't want to do this in your office with actual vaccine.

The sprayer produces a very fine mist. The mist is not uncomfortable for the person being vaccinated. If the person should sneeze or cough during or after administration, the dose does NOT need to be repeated. Administration of LAIV is also a new skill to vaccine providers. Although spraying the dose into the nose is not difficult, it may seen awkward the first time or two that you administer the vaccine. MedImmune produced a short video that describes the steps involved in administering the vaccine. Have a look.

> Let's look at how you administer America's first nasal flu vaccine in five steps. Step one is thawing. Remove the frozen FluMist from the freezer. Hold the sprayer in the palm of your hand for approximately one to three minutes until the vaccine is thawed. You must use this vaccine immediately. You can thaw it just before administration while getting your patients settled in the exam room.
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> Please note, do not roll the sprayer between the palms of your hands to thaw. Rolling the sprayer could cause the dose divider clip or the plunger to separate from the sprayer. If you prefer, you can thaw it by placing it directly into the refrigerator. However, you must discard any vaccine that is not used within 24 hours of being thawed in the refrigerator. And here's something you should know.

When FluMist is thawed, it's a colorless to pale yellow liquid. You may see some particulates, but these do not affect the use of the product.

Step two, remove the rubber tipped protector from the end of the FluMist applicator. Tell your patients to breathe normally. They don't need to inhale the FluMist vaccine. They can just breathe naturally. Step three. While the patient is seated in an upright position with the head tilted back, place the tip of the FluMist applicator just inside the nostril. This helps ensure FluMist is delivered into the nose. Then depress the plunger. Step four. Remove the divider clip from the plunger. Discard the clip. And lastly, step five. Place the tip of the applicator just inside the other nostril and depress the plunger, delivering the second vaccine to the remaining nostril.

Once FluMist has been administered, you should dispose of the sprayer in an impenetrable container. Let's review. Step one, thaw this the palm of the hand for about one to three minutes. Step two, remove the rubber-tip protector. Tell your patients to breathe normally. They don't need to inhale the FluMist vaccine. They can just breathe naturally. Step three, with the patient in an upright position with the head tilted back, place the tip of the applicator just inside the nostril. Then depress the plunger. Step four, remove the dose divider clip and discard. Step five – last step – place the tip the applicator just inside the second nostril and depress the plunger. Then dispose of the used sprayer in an impenetrable sharp container.

Remember these five tests for administering FluMist. Step one, thaw the sprayer. Step two, remove the rubber tip protector. Step three, mist the first nostril. Step four, remove the dose divider clip. Step five, mist the second nostril and dispose of the sprayer.

To sum up, live attenuated influenza vaccine is a new product that will compliment, but NOT REPLACE inactivated influenza vaccine. The most important thing to remember is that it is approved ONLY for healthy people 5 through 49 years of age. LAIV must not be administered to children younger than 5 years, adults 50 and older, or to anyone with a medical condition that places them high risk for complications of influenza. These groups should receive inactivated influenza vaccine.

The vaccine is extremely fragile, and requires special storage conditions that you must plan very carefully. Supplemental ACIP recommendations for LAIV are being finalized, and publication is anticipated in September 2003. We will put a link to the publication on our broadcast resources web page as soon as the document is available.

A new influenza Vaccine Information Statement specific to LAIV is being developed. We expect it to be approved and ready to distribute in September. As soon as we have it ready, it will be posted on our VIS website, and on our broadcast resource web page.